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REVIEW ARTICLE

Bioactive compounds from *Cordyceps* and their therapeutic potential

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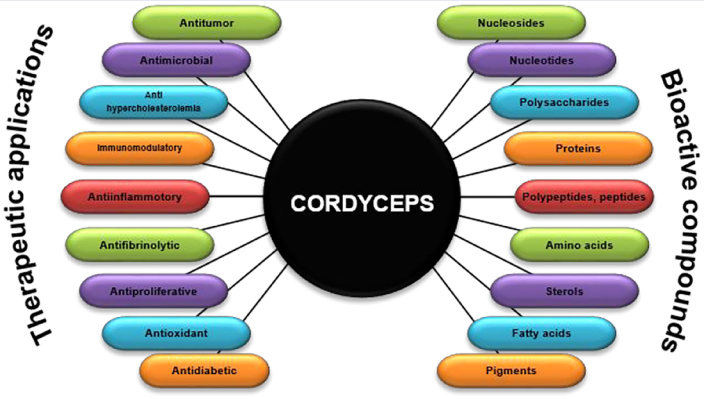
ABSTRACT

The Clavicipitaceae family's largest and most diverse genus is *Cordyceps*. They are most abundant and diverse in humid temperate and tropical forests and have a wide distribution in: Europe, North America, and East and Southeast Asian countries, particularly: Bhutan, China, Japan, Nepal, Korea, Thailand, Vietnam, Tibet, and the Himalayan region of India, and Sikkim. It is a well-known parasitic fungus that feeds on insects and other arthropods belonging to 10 different orders. Over 200 bioactive metabolites, that include: nucleotides and nucleosides, polysaccharides, proteins, polypeptides, amino acids, sterols, and fatty acids, among others have been extracted from *Cordyceps* spp. demonstrating the phytochemical richness of this genus. These components have been associated with a variety of pharmacological effects, including: anti-microbial, anti-apoptotic, anti-cancer, anti-inflammatory, antioxidant, and immunomodulatory activities. In this paper, the bioactivity of various classes of metabolites produced by *Cordyceps* spp., and their therapeutic properties have been reviewed in an attempt to update the existing literature. Furthermore, one of its nucleoside and a key bioactive compound, cordycepin has been critically elaborated with regard to its biosynthesis pathway and the recently proposed protector-protégé mechanism as well as various biological and pharmacological effects, such as: suppression of purine and nucleic acid biosynthesis, induction of apoptosis, and cell cycle regulation with their mechanism of action. This review provides current knowledge on the bioactive potential of *Cordyceps* spp.

GRAPHICAL ABSTRACT



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Introduction

Medicinal mushrooms have been explored for their bio-metabolites since ancient times and are used to cure a variety of ailments [1]. *Cordyceps* is a popular genus of medicinal fungus with a valuable reservoir of varied natural compounds as well as distinct biological functions. With 750 species, the genus *Cordyceps* ecosystems across the world. The presence of many species under various environmental circumstances across the world illustrates their worldwide dispersion [6–9]. It is a renowned ascomycete parasitic fungus, with all identified species functioning as endoparasitoids, primarily on insects and other arthropods, but also on a few other fungi. Only 35 of the 750 *Cordyceps*

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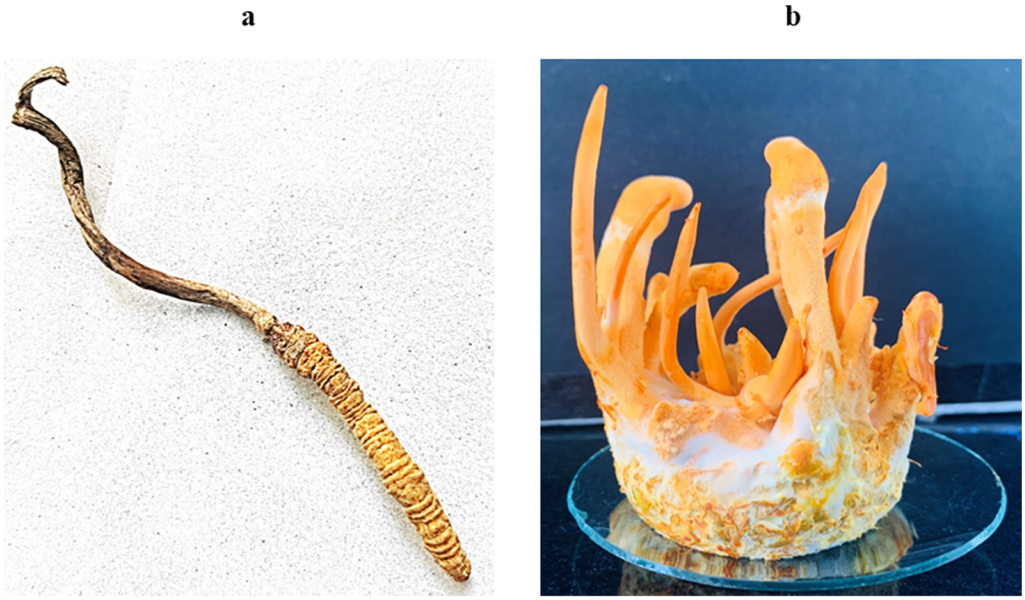

Figure 1. a. *Cordyceps sinesis* (=*Ophiocordyceps sinensis*) (Purchased from Stoic Enterprises, Paschim Vihar, New Delhi, Delhi. https://www.cordycepselixir.com); b. Solid state fermentation of *Cordyceps militaris* in Jar bottles (Brown rice media - 60 days) with fruiting bodies.

species known have been documented to be utilized: as a folk medicine therapy, as a bioactive, or to have a report on its identification [10]. *C. sinensis* (now identified as *Ophiocordyceps sinensis* due to the reassignment of the species to the family Ophiocordycipitaceae) (Figure 1a), *C. militaris* (Figure 1b), *C. sobolifera*, *C. subssesilus*, *C. ophioglossoides*, and other *Cordyceps* species are currently being cultivated for medical uses and usage in health supplements. They comprise a variety of bioactive compounds, such as: nucleotides, amino acids, polysaccharides, flavonoids, proteins, and sterols, which endow it with a variety of health-improving properties, such as: antioxidant, anti-aging, immunoenhancer, neuro-cardioprotective, anti-metastatic, hepatoprotective, tonic effect, and so on [11,12]. This review is focused on providing up-to-date information on the wide range of bioactive compounds produced by various *Cordyceps* spp. along with their pharmacological applications. It is expected that this work will provide a ready reference for researchers trying to develop *Cordyceps*-based products for pharmacological and nutraceutical applications.

Bioactive compounds from *Cordyceps*

Different species of *Cordyceps* have been used for various nutraceutical applications. Mechanisms of action of some of these therapeutic properties are summarized in Figure 2. All the different biomolecules were grouped based on their structural similarity and are discussed in this section.

Nucleosides

Nucleosides comprise a nitrogenous base (nucleobase) and a 5-carbon ribose or deoxyribose sugar. Nucleosides are one of the significant bioactive compounds employed as a chemical marker for quality assurance of *Cordyceps* [13]. Different nucleosides, like: Adenosine (Figure 3a –1), Adenine, Cordycepin (3′-deoxyadenosine) (Figure 3a – 2), 2′-Deoxyadenosine, 2′3′-Dideoxyadenosine, 2′-Methoxydenosine, *N*6-(2-hydroxyethyl)-Adenosine (Figure 3a – 3), 3′-Amino-3′- deoxyadenosine, Hypoxanthine, Uridine, Uracil, 2′-Deoxyuridine, 3′-Methoxyuridine, Inosine (Hypoxanthin), Guanosine, Deoxyguanosine, Guanine, Cytosine, Cytidine, Thymidine, and Thymine have been reported to be found in different species of *Cordyceps* [14–21]. Profiling of nucleosides and their associated molecules is used as a chemical marker for *Cordyceps* and derived products are quite common practice for quality assurance. In the following sections, *Cordyceps*-derived nucleosides, and their bioactivities are discussed.

Cordycepin

Due to the various biological and pharmacological properties of cordycepin, it has gained much attention in the recent times. The following sections, therefore, elaborates the biosynthesis of cordycepin along with various pharmaocological applications.

Cordycepin, chemically identified as 3′-deoxyadenosine, is an adenosine analog (short of a 3′ hydroxyl group) and is the most important nucleoside, first isolated in the

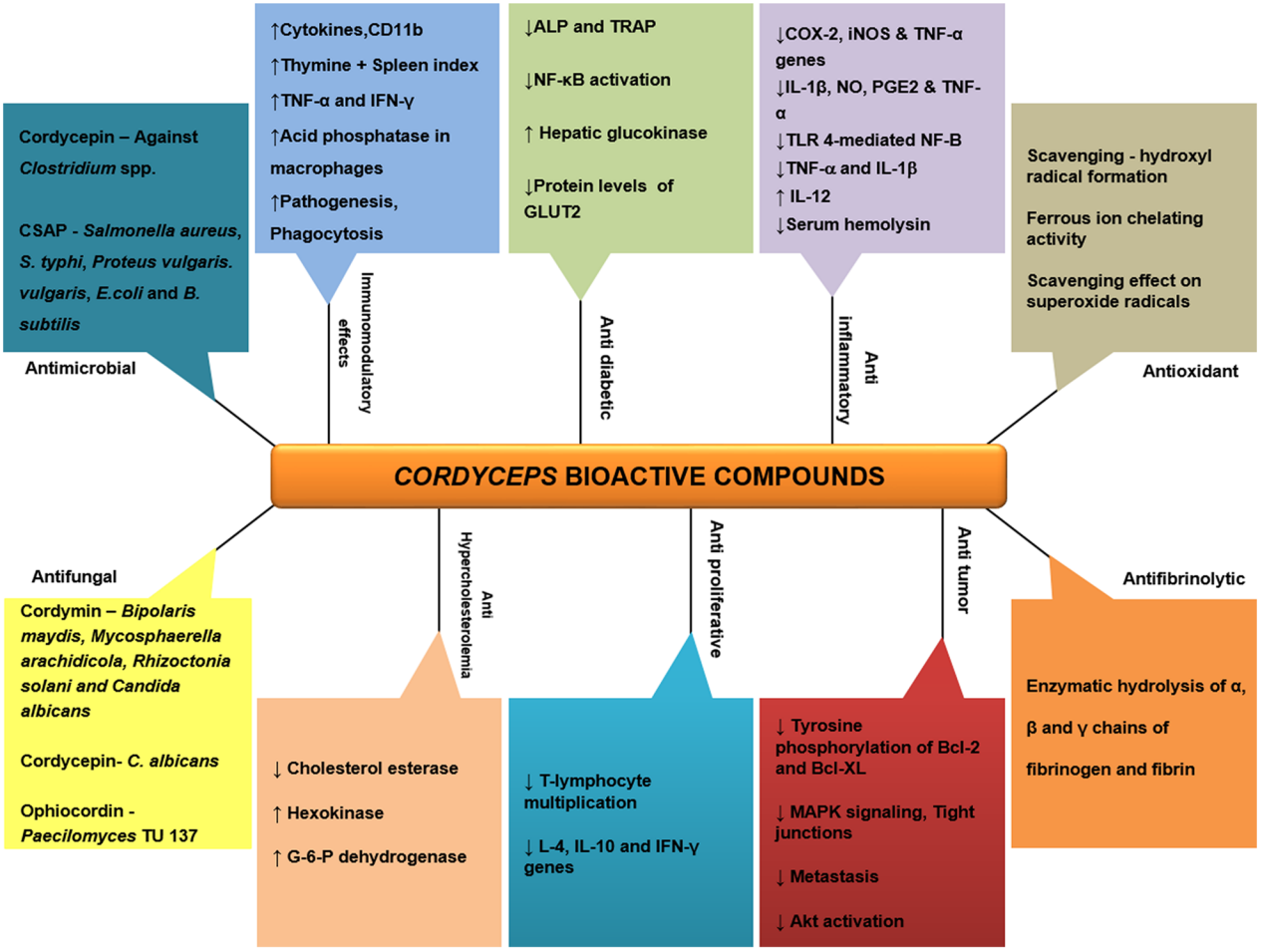

Figure 2. Various bioactive compounds obtained from *Cordyceps* spp. shows a wide range of therapeutic properties. This figure depicts a various reported therapeutic applications of bioactive compounds from *Cordyceps* spp. such as – (i) Immunomodulatory, (ii) Anti-diabetic, (iii) Anti-inflammatory, (iv) Anti-tumor, (v) Anti-proliferative, (vi) Hypocholesterolemic, (vii) Antimicrobial, (viii) Antifungal, (ix) Antioxidant and (x) Antifibrinolytic activity along with their respective molecular mechanisms of action as proposed in various clinical studies.

early 1950s from *C. militaris.* Later, in 1996, using technologies like infrared spectroscopy (IR) and nuclear magnetic resonance (NMR) the structure of cordycepin was fully characterized. The molecular formula was identified to be $C_{10}H_{13}N_5O_3$ with a molecular weight of 251.24. It is alkaline and has a needlelike flaky crystal structure. The melting point of cordycepin was found to be 228 °C–231 °C and maximum absorption (λ_{max}) were recorded at 259.0 nm [22]. Structurally cordycepin comprises a purine (adenine) nucleoside connected to a ribofuranose moiety through a β-N9-glycosidic bond [23]. The molecular structure of the cordycepin is provided in Figure 3A. In addition to *C. militaris*, *Aspergillus nidulans* [24], *C. kyushensis* Kob [25] may all produce cordycepin.

Biosynthesis of cordycepin

Lennon and Suhadolnik [26] first reported the *in-vivo* biosynthesis of cordycepin in 1976 by tracking purine metabolism pathways *via* [U- 14C] adenosine and [3- 3H] ribose labels to monitor the 3H/14C ratio. The results indicated that cordycepin was formed from adenosine by a ribonucleotide reductase mediated reductive mechanism and there is no adenine-ribose bond cleavage in the process as in the case of 2′deoxynucleotides synthesis. It has been suggested that the ribonucleotide reductase might undergo a modification before participating in the cordycepin biosynthesis to isolate this process from the formation of 2′deoxynucleotides for DNA synthesis. As a result, cordycepin biosynthesis does not commence until DNA synthesis has ended [26].

The key regulatory genes of cordycepin biosynthesis were not known until 2017 when Xia et al. [27] identified: *cns1*, *cns2*, *cns3*, and *cns4* as four highly conserved genes in *C. militaris* and *A. nidulans,* both of which are reported to produce cordycepin [24]. These four genes were found to be clustered with each translated protein forming a conserved domain in the cordycepin metabolism machinery. Cns 1 is an

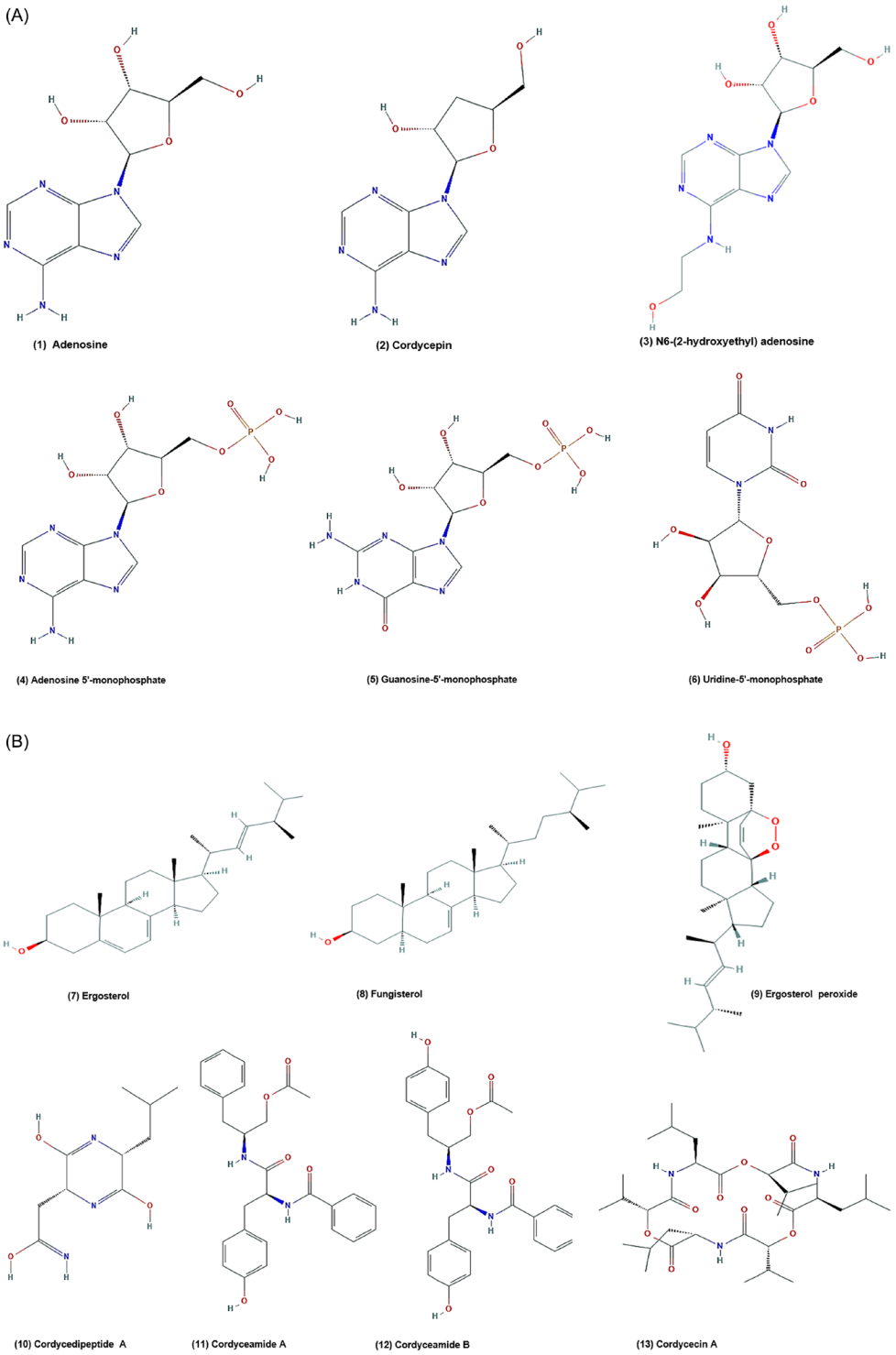

Figure 3. a. Collection of the molecular structures of different metabolites and bioactive compounds reportedly isolated from different *Cordyceps* spp. (1) Adenosine, (2) Cordycepin, (3) N6-(2-hydroxyethyl)adenosine, (4) Adenosine 5′-monophosphate (AMP), (5) Guanosine-5′-monophosphate (GMP), (6) Uridine-5′-monophosphate (UMP). All the structures are given unique numbers corresponding to the numbers in parenthesis next to the name of the compound mentioned in the main text. Source: https://pubchem.ncbi.nlm.nih.gov/. b. Collection of the molecular structures of different metabolites and bioactive compounds reportedly isolated from different *Cordyceps* spp. (7) Ergosterol, (8) Fungisterol, (9) Ergosterol peroxide, (10) Cordycedipeptide A, (11) Cordyceamide A, (12) Cordceamide B, (13) Cordycecin A. All the structures are given unique numbers corresponding to the numbers in parenthesis next to the name of the compound mentioned in the main text. Source: https://pubchem.ncbi.nlm.nih.gov/. c. Collection of the molecular structures of different metabolites and bioactive compounds reportedly isolated from different *Cordyceps* spp. (14) Ophiocordin, (15) Bioxanthracene, (16) Cordycepin acid, (17) Cordycepol A, (18) Cordycepol B, (19) Cordycepol C. All the structures are given unique numbers corresponding to the numbers in parenthesis next to the name of the compound mentioned in the main text. Source: https://pubchem.ncbi.nlm.nih.gov/

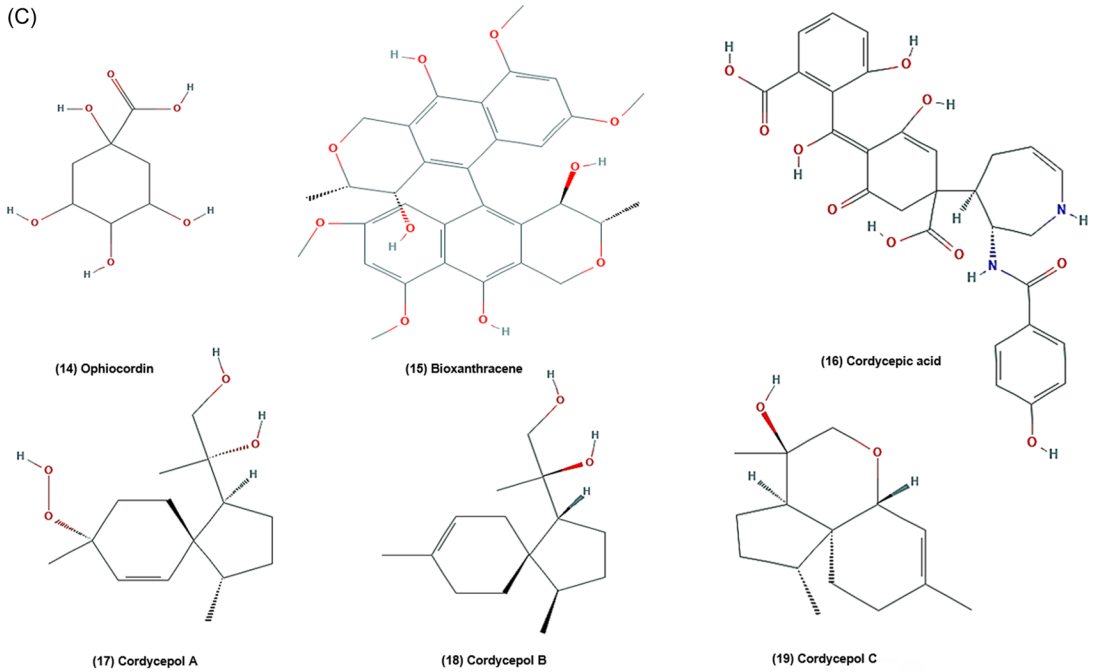

Figure 3. Continued.

oxidoreductase/dehydrogenase domain, Cns 2 is a metal-dependent phosphohydrolase domain of the HDc family, and Cns 3 has an N-terminal nucleoside/nucleotide kinase domain along with an ATP phosphoribosyltransferases domain of his family, and Cns 4 is an ATP binding cassette (ABC) transporter.

The biosynthesis begins with the conversion of glucose by the pentose phosphate pathway into glucose-6-phosphate and subsequently to ribose-5-phosphate which is a vital substrate in the *de novo* purine nucleotide pathway. Ribose-5-phosphate is converted to AMP and GMP with phosphoribosyl pyrophosphate and IMP as intermediate products. The precursors for the nitrogen base residue are glutamine and glycine [28,29]. Adenylate kinase phosphorylates AMP to ADP which is further transformed to 3'deoxyadenosine 5'diphosphate by ribonucleotide reductase. Adenylate kinase further converts 3'-deoxyadenosine 5'-diphosphate to 3'-deoxyadenosine 5'-phosphate. Although the bioconversion of adenosine to cordycepin is not fully known, hypothetically, 5' nucleotidase is believed to convert 3'-deoxyadenosine 5'-phosphate to cordycepin [30]. Some of the key hypothetical regulatory enzymes are: (i) Phosphoribosylamidotransferase (PRAT) – known to be the rate-limiting enzyme for purine metabolism, and (ii) IMP cycloehydrolase (IMPC) which produces IMP (Inosine monophosphate), IMP deh ydrogenase which oxidizes IMP to produce GMP, and (iii) Adenylosuccinate synthetase that regulates AMP production [31–33].

Alternatively, 3' hydroxyl of the adenosine which is obtained from inosine of the IMP as well as other nucleotide pathways is phosphorylated by Cns 3 with its nucleotide/nucleoside kinase domain to form adenosine 3'-monophosphate (3'AMP). Cns 2 further dephosphorylates 3'-AMP to 2'-carbonyl-3'-deoxyadenosine (2'-C-3'-dA) with its phosphohydrolase domain. Cns 1 finally converts 2'-C-3'-dA to cordycepin with its oxidoreductase domain. As a result, *cns1* and *cns2* are considered indispensable genes for cordycepin biosynthesis, and inhibition of either of them leads to absolute cordycepin deficiency in *C. militaris*

Cordycepin accumulation can reach cytotoxic levels and thereby shut down the biosynthesis machinery. To overcome this, a protector-protégé mechanism was reported by Wu et al. [34], where biosynthesis of pentostatin by phosphoribosyltransferase domain of Cns 3, an adenosine analog with adenosine deaminase inhibitory activity was coupled with cordycepin biosynthesis such that it maintained the production of cordycepin by deaminase mediated conversion of cordycepin to the nontoxic 3'-deoxyinosine, which is then pumped out of the cell by the action of ABC transporter domain of Cns 4. This mechanism is triggered when cordycepin concentration in the cell reaches toxic levels [34]. The complete biosynthesis pathway of cordycepin has been shown in Figure 4.

Pharmacological applications of the Cordycepin

Anti cancer properties

In caspase-based mechanisms, cordycepin can prompt the apoptosis of cancer cells. Activation of caspase, the association of Fas and FADD (Fas-associated

protein with death domain), and regulation of Bid and tBid of Bcl-2 family protein levels were the causes of apoptosis of human liver cancer (HepG2) cells [35]. In addition, it reduced the survival of human bladder cells (T24 cells) by stimulating the A3 adenosine receptor and subsequently suppressing the Akt pathways increasing cleaved Caspase-3 and apoptosis [36]. Cordycepin has also been reported to trigger the MKK7-JNK (Mitogen activated protein kinase kinase – c-Jun NH2-terminal kinase) signaling system, contributing to the triggering of the Bax/caspase-3/PARP (Poly ADP-ribose polymerase) mediated pathways and apoptosis in human renal cells *via* inhibiting the anti-apoptotic protein cell caspase 8 (FLICE)-like

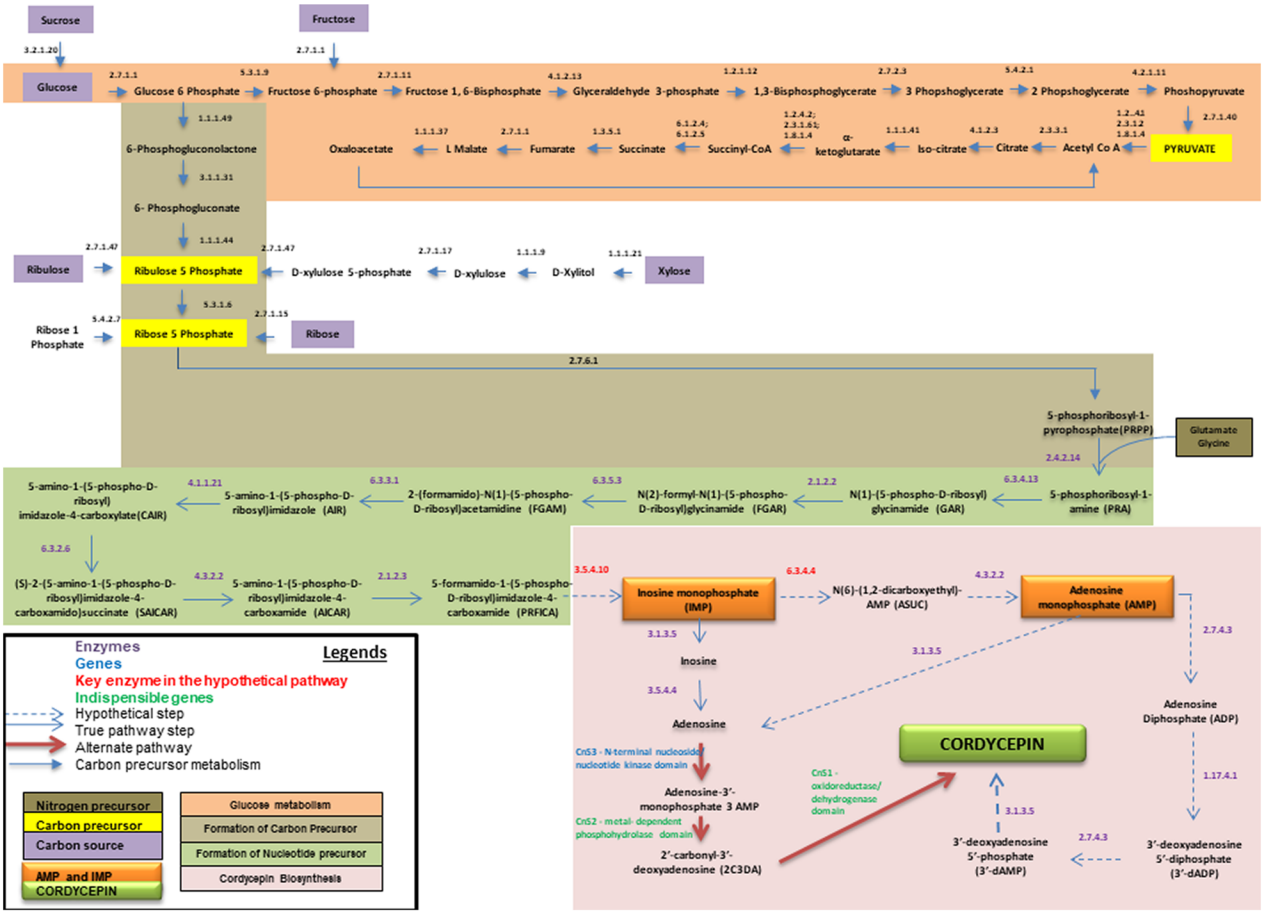

Figure 4. A detailed description of the biosynthetic pathway for Cordycepin is depicted in this figure. Various phases of the biosynthesis starting from carbon sources and precursors and ending with Cordycepin are described with the use of several legends mentioned in the figure. It is important to note that the conversion of AMP to Cordycepin may be explained by a series of hypothetical transformations of the nucleotide or through the more recently reported alternative pathway governed by indispensable genes coding for various domains of enzymes needed for bioconversion of Adenosine to Cordycepin. The enzymes for every reaction in the pathway are Alpha-glucosidase/Glucoinvertase (3.2.1.20); Hexokinase (2.7.1.1); Glucose-6-phosphate isomerase (5.3.1.9); 6-phosphofructokinase (2.7.1.11); Fructose-bisphosphate aldolase (4.1.2.13); Glyceraldehyde 3-phosphate dehydrogenase (1.2.1.12); Phosphoglycerate kinase (2.7.2.3); Phosphoglycerate mutase (5.4.2.1); Enolase (4.2.1.11); Pyruvate kinase (2.7.1.40); Pyruvate dehydrogenase complex (1.2.4.1; 2.3.1.12; 1.8.1.4); Citrate (Si)-synthase (2.3.3.1); Aconitate hydratase (4.2.1.3); Isocitrate dehydrogenase (1.1.1.41); α-ketoglutarate dehydrogenase complex (1.2.4.2; 2.3.1.61; 1.8.1.4); Succinyl coenzyme A synthetase (6.1.2.4; 6.1.2.5); Succinate dehydrogenase (1.3.5.1); Fumarate hydratase (4.2.1.2); Malate dehydrogenase (1.1.1.37); Glucose 6-phosphate-1-dehydrogenase (1.1.1.49); 6-Phosphogluconolactonase (3.1.1.31); 6-Phosphogluconate dehydrogenase (1.1.1.44); D-ribulokinase (2.7.1.47); Aldose reductase (1.1.1.21); D-xylulose reductase (1.1.1.9); Xylulose kinase (2.7.1.17); Phospho ribomutase (5.4.2.7); Ribokinase (2.7.1.15); Ribulose-phosphate 3-epimerase. (2.7.1.47); Ribose-phosphate diphosphokinase (2.7.6.1); Amidophospho ribosyltransferase (2.4.2.14); Glycinamide ribonucleotide synthetase (6.3.4.13); Phosphoribosyl glycinamide formyltransferase 1 (2.1.2.2); Phosphoribosylformylglycinamidine synthase (6.3.5.3); Phosphoribosyl formylglycinamidine cyclo-ligase (6.3.3.1); Phosphoribosylaminoimidazole carboxylase (4.1.1.21); Phosphoribosylaminoimidazolesuccinocarboxamide synthase (6.3.2.6); Adenylosuccinate lyase (4.3.2.2); Phosphoribosylaminoimidazolecarboxamide formyltransferase (2.1.2.3); IMP cyclohydrolase (3.5.4.10); Adenylosuccinate synthase (6.3.4.4); Adenylosuccinate lyase (4.3.2.2); Adenylate kinase (2.7.4.3); Ribonucleoside-diphosphate reductase (1.17.4.1); 5'- nucleotidase (3.1.3.5); Adenosine deaminase (3.5.4.4).

inhibitory protein production [37]. Additionally, cordycepin stimulates apoptosis in cancer cells by independent caspase mechanisms. In an oral tumor mouse model, cordycepin has been reported to lower the cell mitosis and signaling of EGFR (Epidermal growth factor receptor). In line with this, the therapy with cordycepin greatly decreased the levels of EGFR and the proliferation marker protein ki-67 signaling molecules to cause cancer cells' apoptosis [38]. Cordycepin mediated cancer cell apoptosis with CAV1 (caveolin-1) upregulated JNK/Foxo3a (Forkhead transcription factor) signaling pathway for human lung adenocarcinoma and substantially reduced tumor size in nude mice [39]. Treatment involving cordycepin assisted the discharge of cytochrome c into the cytosol from mitochondria further activated caspase-9 and facilitated cell apoptosis in U937 and NB-4 cells. The augmented p53 expression by cordycepin also hinders the cyclin A2, cyclin E, and CDK2 expression, which, through the activation of the Chk2-Cdc25A pathway, contributes to the aggregation of cells in the S phase [40]. Cordycepin induces apoptosis in human bladder cancer T24 cells through activating intrinsic and extrinsic apoptosis pathways as well as the ROS-dependent inactivation of PI3K/Akt (Protein kinase B) signaling [41].

Cordycepin also decreased cell proliferation, slowed migration, and caused apoptosis in human lung cancer cells - A549 cells and NCI-H460 cells, resulting in inhibitory effects on the development of human lung cancer [42]. The *Cordyceps militaris* preparation (CMP) and its component cordycepin have been proven in a mouse model of oral cancer to decrease tumor development and malignant transformation by inhibiting EGFR and IL-17RA signaling and increasing anti-tumor immunity [38]. Cordycepin suppresses CCL5 (Chemokine ligand 5) mediated Akt/NF-κB signaling in SKOV-3 cells, which upregulate caspase-3 activation, indicating that cordycepin might be used to treat ovarian cancer [43]. Cordycepin suppressed cell survival, multiplication, and colony formation in human pancreatic cancer cells (MIAPaCa-2 and Capan-1) and triggered cell cycle arrest and early apoptosis in a dose and time-dependent manner. *In vitro* and *in vivo*, decreased and upregulation of Bax, cleaved caspase-3, caspase-9, and PARP, besides downregulation of Bcl-2, suggested that cordycepin's anticancer action was mediated through the mitochondria-mediated intrinsic route [44]. Cordycepin is said to prevent the cancer cell's propagation in the esophagus by instigating apoptosis and ERK (Extracellular signal-regulated kinases) pathway inactivation to arrest G2/M, thereby revealing that cordycepin helps in anti-proliferation and pro-apoptosis mechanisms in cancer cells [45]. Cordycepin substantially decreased the levels of: NF- κB, TLR4 (Toll-like receptor 4), COX2 (cyclooxygenase-2), TNF-α (Tumor necrosis factor alpha), and IL-1 in HEK293T cells. Cordycepin, on the other hand, could no longer impact the levels if TLR4 was silenced. *C. militaris* slowed the development of CKD by altering the TLR4/NF-B lipid and redox signaling pathways *via* cordycepin [46].

Other pharmacological effects

Anti-dengue – Cordycepin (isolated from *C. militaris*) blocks Dengue virus (DENV) replication by binding to DENV nonstructural protein 5 (NS5), an essential RNA synthesis enzyme, at both the methyltransferase (MTase) and RNA-dependent RNA polymerase (RdRp) domains, indicating its prospective as an anti-dengue treatment [47].

Cardiac hypertrophy – Cordycepin (isolated from *C. militaris*) brought down cardiac hypertrophy through activating protein kinase (AMPK) signaling and attenuating oxidative stress in both cordycepin-treated mice and cardiomyocytes *in vitro* [48].

Cardio protectant – Cordycepin protected diabetic hearts (in diabetic mice) against myocardial ischemia/reperfusion (MI/R) injury in an *in vitro* study *via* AMPK/Mfn2-dependent mitochondrial fusion, which adds to cordycepin's cardioprotective action [49].

Neuroprotective effects – Cordycepin improved cognitive impairments post cerebral ischemia by maintaining dendritic morphology and synaptic function, an effect facilitated by Adenosine A1 receptors (A1R) [50].

Herbicidal property – Cordycepin produced phytotoxicity against *Raphanus sativus* by lowering photosynthetic pigments and increasing: electrolyte leakage, lipid peroxidation, proline, total phenolic, and total flavonoid levels, and so has the potential to be utilized as a powerful plant growth inhibitor [51].

Anti allergic effect - In both *in vitro* and *in vivo* investigations, Phull et al. [52] examined the effects of *Pediococcus pentosaceus* (SC11) fermentation on the improvement of the anti-allergic potential of *C. militaris* cultivated on germinated *Rhynchosia nulubilis* (GRC) against a type I hypersensitivity reaction. After SC11 fermentation, GRC had considerably more cordycepin and overall antioxidant capacity. When compared to GRC, GRC-SC11 greatly improved anti-allergic responses by blocking IgE/antigen-induced degranulation in RBL-2H3 cells [52].

Apart from these, various other pharmacological and therapeutic properties of cordycepin are mentioned in Table 1.

Adenosine

The other important nucleoside next to cordycepin produced by *Cordyceps* spp. is adenosine, which plays a predominant role in the biochemical processes of living organisms and is recognized as an important chemical marker [3]. Adenosine ($C_{10}H_{13}N_5O_4$; MW: 267.24 g/mol) is composed of ribonucleoside attached to a ribofuranose moiety with the help of β-N (9)-glycosidic bond. Adenosine analogues, such as: 2′-deoxyadenosine ($C_{10}H_{13}N_5O_3$; MW: 251.2419 g/mol), 2′3′-dideoxyadenosine ($C_{10}H_{13}N_5O_2$; MW: 235.24 g/mol), cordycepin triphosphate ($C_{10}H_{16}N_5O_{12}P_3$; MW: 491.18 g/mol), 3′-amino-3′-deoxyadenosine ($C_{10}H_{14}N_6O_3$; MW: 266.26 g/mol) have also been detected exclusively in *Cordyceps* spp. [9,13]. In the laboratory cultivated *C. sinensis*, the adenosine content is much greater than the natural ones and in cultivated *C. militaris* in laboratory conditions [15].

The adenosine extraction ratio is significantly affected by extraction time, and it is believed that certain enzymes that can decompose adenosine may be present in natural *C. sinensis* [53]. It is a predominant cell energy transport and signal transduction agent and can also avoid tissue injury, for example, chronic heart disease therapy, anti-inflammatory effects, and anticonvulsant activity [54–57]. Adenosine can also act as a cell growth suppressor by activating caspases with mitochondria-related and/or independently through various intrinsic and extrinsic signaling pathways [58–60]. Adenosine mediates its effects by activating the GPCR (G-protein coupled receptors) family: A1, A2A, A2B, and A3 [61]. In depression, locomotion, and anxiety, adenosine 2 A play a significant role [62]. Furthermore, adenosine operates on one or more receptors and plays a key role in: immune, inflammation, defense, and repair of the dermal tissue.

Table 1. Pharmacological and therapeutic properties of Cordycepin.

Source	Property	Effects	References
C. militaris	Anti-microbial property	Inhibited pathogens - *Staphylococcus aureus, Klebsiella pneumonia*	[123]
C. militaris	Antifungal activity	Antifungal activity against *Aspergillus niger and Trichophyton rubrum*	
C. militaris capsule	Anti viral	In combination with interferon-a and/or ribavirin, it increased anti-HCV (persistent hepatitis C virus) activity	[124]
Commercial Cordycepin from Sigma Chemical Co. (St. Louis, MO, USA)	Anti viral	Antiviral activity against Epstein-Barr virus by Inducing histone modification at EBV genomic loci inhibits EBV protein synthesis and the production of EBV progeny.	[125]
Commercial Cordycepin from Sigma Chemical Co. (St. Louis, MO, USA)	Anti-metastatic activity	Inhibits TPA-induced MMP-9 expression. Obstructs - Capability of AP-1 activation via MAPK signaling pathway in MCF-7 cells	[126]
Cordycepin (Sigma-Aldrich Chemical Co., St Louis, MO, USA)	Anti-invasive activity	Prevent the relocation and incursion of LNCaP cells (human prostate carcinoma) via the downregulation of TJs (tight junctions) and MMP activity, perhaps in conjunction with Akt activation suppression	[127]
	Anti-Platelet aggregation	Prevents U46619- induced platelet aggregation by lessening free $[Ca^{2+}]i$ and aggregation-inducing autacoidal molecule throm-boxane $A_2(TXA_2)$ generated in different agonist-activated platelets	[128]
Water extracts of *C. sinensis* (WECS)	Anti-Cancer	Stimulation of adenosine A3 receptor. Activation of Glycogen synthase kinase (GSK)-3b. Suppression of cyclin D1.	[129]
	Antimetastatic activity	Inhibiting the activity of matrix metalloproteinase (MMP)-2 and MMP-9, as well as accelerating the production of tissue inhibitor of metalloproteinase (TIMP)−1 and TIMP-2 from cancer cells.	
Not available	Anti inflammatory activity	Restrained the production of NO and PGE2 stimulated by IL-1β. ↓ In OA chondrocytes, IL-1β promoted gene expression and production of COX-2, iNOS, IL-6 and MMP-13 Reduced NF-κB activation produced by IL-1β by restraining the breakdown of its inhibitory protein nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκB-α) in the cytoplasm	[130]
Commercial Cordycepin from Sigma Chemical Co. (St. Louis, MO, USA)	Antidiabetic activity	Restrained NF-κB activation in LPS-activated macrophages that suppressed T2D (type 2 diabetes) regulating genes	[131]
Cordycepin from Chinese Academy of Medical Sciences & Peking Union Medical College	Hypoglycemic/ Anti-Cholesterol activity	↓Plasma glucose levels, hyperphagia, polydipsia, and body weight; ↑Hepatic glycogen content and oral glucose tolerance	[132]
C. militaris		Avoids hyperlipidemia by activation of AMPK (phospho–AMP-activated protein kinas) pathway and lipid biosynthesis inhibition	[133]
Commercial Cordycepin from Sigma Chemical Co. (St. Louis, MO, USA)	Anti - cancer	Supressed cell growth in HCT116 and Caco-2 by down-regulating MYC mRNA/ protein expression up-regulating miR-26a	[134]
Cordycepin from Sigma (St. Louis, Missouri).		Subdued - cell growth, invasion, and caused apoptosis in osteosarcoma cells. ↑ Osteosarcoma cell susceptibility to cisplatin by stimulating AMPK and blocking the AKT/mTOR signaling pathway.	[135]
Cordycepin from (Santa cruz; Biotechnology)		Inhibited migration, invasion and lowered the expression of c-X-c chemokine receptor type 4 (cXcR4); nuclear translocation of P65 by preventing p-IB activation; attenuated reactivity to stromal cell-derived factor 1 (SdF1)	[136]

N6-(2-hydroxyethyl) adenosine (HEA)

N6-(2hydroxyethyl)-adenosine (HEA) ($C_{12}H_{17}N_5O_5$; MW: 311.294 g/mol) was first isolated in 1987 from cultured *C. pruinosa* mycelia, which acts as a Ca^{2+} competitor, an inotropic agent and has resistance against radiation, and is one of the key bioactive compounds [63]. HEA causes hypomobility in mice [64], and it can form a complex after binding with human serum albumin (HSA) by hydrophobic interaction [65]. The pharmacological properties of HEA are mentioned in Table 2.

Other nucleosides

Guanosine ($C_{10}H_{13}N_5O_5$; MW: 283.24 g/mol), a purine nucleoside made from a β-N9-glycosidic bond linking a ribose ring and guanine and is needed for metabolism. It is often found in some *C. cidae* [66] and *Ophiocordyceps xuefengensis* [67] along with other nucleosides and can be separated and determined by HPLC –UV [15] or UPLC [19]. Guanosine, as well as its analogs, play essential roles in diverse biochemical pathways, for instance, (i) synthesis of nucleic acid and proteins, (ii) photosynthesis, (iii) intracellular signal transduction, and (iv) muscle contraction [13]. Uridine ($C_9H_{12}N_2O_6$; MW: 244.2 g/mol) is a glycosylated pyrimidine-analog having uracil connected to a ribose ring *via* a β-N_1-glycosidic bond found in *C. jiangxiensis*. Two uridine analogs 2′-deoxyuridine ($C_9H_{12}N_2O_5$; MW: 228.202 g/mol) and 3′-O-methyluridine ($C_{10}H_{14}N_2O_6$; MW: 258.23 g/mol), were found in the butanol extractions of *Penicillium jiangxiense* mycelium, the anamorph of medicinal *C. jiangxiensis*. However, their biological activity was not reported. Cytidine ($C_9H_{13}N_3O_5$; MW: 243.22 g/mol) is a pyrimidine nucleoside that is comprised of a cytosine bound to ribose *via* a β-N1-glycosidic bond. Only a few *Cordyceps* species have been reported that contain cytidine along with other nucleosides [9]. Thymidine ($C_{10}H_{14}N_2O_5$; MW: 242.23 g/mol), or deoxythymidine or thymine deoxyriboside is another pyrimidine nucleoside having a pyrimidine base thymine attached to the sugar deoxyribose and is commonly found in many *Cordyceps* spp. [9,13].

Table 2. Pharmacological and therapeutic properties of N6-(2hydroxyethyl)-adenosine (HEA).

Source of HEA	Property	Effect	References
C. cicadae	Anti-inflammatory activity	Through repressing the toll-like receptor (TLR) 4-mediated nuclear factor-B (NF-B) signaling pathway, the LPS-induced pro-inflammatory reactions were attenuated	[137]
	Antioxidant effect	Against H_2O_2 induced toxicity in PC12 cells	[138]
	Potential therapy renal interstitial fibrosis	Subdual of the NF-κB and TGF-β1/Smad signaling pathway. Lessened UUO-induced inflammation and renal fibroblast activation	[139]
	Anti-hyperglycemic, antioxidant , antiinflammatory effects and kidney protective effects in diabetic rats		[140]

Nucleotides

Yang et al. [14] isolated three nucleotides, namely: uridine-5′-monophosphate (UMP; $C_9H_{13}N_2O_9P$; MW: 324.18 g/mol) (Figure 3a – 06), adenosine-5′-monophosphate (AMP; $C_{10}H_{14}N_5O_7P$; MW: 347.22 g/mol) (Figure 3a – 04), and guanosine-5′-monophosphate (GMP; $C_{10}H_{14}N_5O_8P$; MW: 363.22 g/mol) (Figure 3a – 05) from *Cordyceps* spp. These nucleotides were extracted by ion-pairing reversed-phase liquid chromatography-mass spectrometry (IP-RP-LC-MS) technique [14]. In natural and laboratory cultivated *C. sinensis* and cultivated *C. militaris*, nucleotides such as UMP, GMP and AMP may decompose to uridine, guanosine, and adenosine, correspondingly. In addition, it is possible to further degrade the nucleosides to their bases and/or associated compounds [68].

Polysaccharides

The other important bioactive compounds from *Cordyceps* are the polysaccharides that exist as extracellular and intracellular components. Different species, like: *C. cicadae*, *C. kyushuensis*, *C. militaris*, *C. ophioglossioides*, and *C. sinensis*, produce the polysaccharides. The polysaccharide content, monosaccharide composition, as well as physical, chemical properties, and biological activity, vary for different *Cordyceps* spp. The most prominent monosaccharides that form saccharide polymers are mannose, glucose, and galactose. Hetero polysaccharides like: Exopolysaccharide fraction (EPSF) from *C. sinensis*, acid polysaccharide, PS-A (Glucose: Galactose: Mannose in 2:1:1 ratio) from *Cordyceps sinensis*, polysaccharides like CS-F30 (Galactose: Glucose: Mannose in 62:28:10 ratio), CS-F10 (Galactose: Glucose: Mannose in 43:33:24 ratio) from *C. sinensis*, PSCK2-2 (807 kDa; Fructose: Mannose: Rhammose: Galactose: Arabinose in 1.0:1.19:0.11:0.11:0.34 ratio) and PSCK 2-3 (466 kDa; Fructose: Mannose: Rhammose: Glucose Arabinose in 1:1.29:0.14:0.07:0.32 ratio), from

C. kyushuensis, CPS-1 (Rhammose: Xylose: Mannose: Glucose: Galactose in 1:6.43:25.6:16.0:13.8 ratio) from *C. militaris*, Water-soluble polysaccharide CPS-2 (mannose: glucose: galactose in 4:11:1 ratio) from *C. sinensis,* CPS (Rhammose: Arabinose: Xylose: Mannose: Glucose: Galactose in 3.0:2.6:1.0:1.3:106.0:2.8 ratio) from *C. gunnii*, Cordysinocan (82 kDa; Glucose: Mannose: Galactose in 2.4:2:1 ratio) from *C. sinensis*, WIPS (1180 kDa) and AIPS (1150 kDa) from *C. sinensis*, EPS-III (1.56×10^3 kDa) from *C. militaris*, CBPS-II (1.273×10^3 kDa) from *C. militaris*, CCP from *C. cicadae*, CMPB90-1 from *C. militaris*, SDQCP-1(19.3 kDa) from *C. militaris*, CSP (*Cordyceps sinensis* polysaccharide) from *C. sinensis* etc. were isolated and their therapeutic properties were studied mentioned in Table 3.

β-D-glucans (β-d-glucose polysaccharides) were extracted and characterized from *Cordyceps* spp. in addition to other polysaccharides. Water-soluble β-Glucan from wild *C. sinensis* having a backbone of (1→3)-β-D-Glcp residues and two (1→6)-β-D-Glcp branches [69]. Similarly, linear β-D-Glcp (1→3)-linked extracted from *C. militaris* shown a greater anti-inflammatory activity by inhibiting the production of IL-1b, TNF-a, and COX-2 [70].

Sterols

Sterols are the other bioactive compounds that are found in *Cordyceps* spp. The two most significant sterols discovered in *Cordyceps* are ergosterol (Figure 3b – 07) and ergosterol peroxide (Figure 3b – 09). Ergosterol is a phytosterol consisting of ergostane ($C_{28}H_{44}O$; MW: 396.6 g/mol) and it is said to be a characteristic fungal sterol having anti-oxidative properties and is an important predecessor of vitamin D2 [71]. Free ergosterol and esterified ergosterol are the two

Table 3. Pharmacological and therapeutic properties of different polysaccharides derived from *Cordyceps* spp.

Compound	Property	Effect	References
EPSF	Immunomodulatory function and antitumour activity	↑Peritoneal macrophage Neutral Red adsorption capacities and spleen lymphocyte multiplication in B16-bearing mice	[141]
EPS	Immunomodulatory effect	↑Cytokine release, CD11b expression, and phagocytosis	[142]
Exopolysaccharide fraction (EPSF)	Immunomodulatory effect	↑Expression of IFN and TNF mRNA in splenic lymphocytes ↑Immunocytes activity in H22 tumor bearing mice	[143]
Acid polysaccharide (APS)	Antioxidant effect	↑ Antioxidant defense capability of the cell PC12 cells are shielded against oxidative damage	[144]
Acid polysaccharide fraction (APSF)	Anti-inflammatory effect	↑ IL-12, TNF-a and iNOS production ↓ IL-10 of Ana-1 cells production	[145]
PSCK2-2 and PSCK 2-3	Antioxidant effect	Scavenging abilities on hydroxyl radicals. Strong capacity on protective effect of DNA damage	[146]
Polysaccharides (PS)	Immunomodulatory effect	↑Thymus and spleen indexes, proliferation of splenic cells, macrophage phagocytosis and levels of TNF-α and IFN-γ	[147]
CPS-1	Anti-inflammatory activity	↓Serum hemolysin formation of mice	[148]
CPS-2	Cure - Renal failure clinically	TGF1 and extracellular matrix (ECM) levels in patients have stabilized	[149]
	Immunomodulatory effect	↓ Cell proliferation caused by PDGF-BB via the TGF-b1/Smad and PDGF/ERK pathways, and it potentially have two way regulatory impacts on the PDGF/ERK cellular signaling pathway	[150]
WIPS and AIPS	Antitumor and immuno-stimulatory effect	Animal studies on melanoma tumor-bearing mice revealed antitumor and immunostimulatory effects	[151]
Cordysinocan	Immunomodulatory effect	↑Effectiveness of phagocytosis and acid phosphatase enzymatic activity in macrophages	[152]
PS-A	Anti-hypercholesterolemia effect	Significant inhibition of cholesterol esterase was seen in an in-vitro enzyme test	[153]
EPS-III	Hypoglycemic effect	Inhibited α-glucosidase effectively alleviate weight loss, ↓ plasma glucose concentrations, ↑glucose tolerance	[154].
CBPS-II	Hypoglycemic effect	Controls the energy metabolism, intestinal flora, and amino acid metabolism disruption	[155].
CCP	Anti-inflammatory and Anti-fibrotic	Suppressed inflammation, renal pathological changes, and renal dysfunction, slowing the progression of renal interstitial fibrosis, modulated gut microbiota dysbiosis ↓ LPS-induced inflammatory cytokine levels and TGF-1-induced fibroblast activation	[156].
CPS	Management of allergic asthma	Inhibited the expression of eotaxin, IL-4, IL-5, IL-13, and IFN- γ in the blood and bronchoalveolar lavage fluid (BALF), Lowered serum IgE levels in mice.	[157].
SDQCP-1	Natural antioxidant and immunomodulator	Activate macrophages to produce NO, TNF-α, IL-6, and IL-10, as well as promote M1 polarization	[158]
CSP (*Cordyceps sinensis* polysaccharide)	Anti-cancer	↓ HCT116 cell growth by inducing apoptosis and blocking autophagy flux, via PI3K-AKT-mTOR and AMPK-mTOR-ULK1 signaling	[159]
(Se)-rich *C. militaris* polysaccharides (SeCMP)	Anti-Hyperlipidemia	Promoted satiety and thermogenesis of obese mice ↓ Gut bacteria, such as *Lactobacillus*, *Dorea*, *Clostridium*, *Ruminococcus* ↑Mucosal beneficial bacteria Akkermansia	[160]

types of ergosterol available. HPLC was used to identify them from *C. sinensis* fruiting bodies and as well the host caterpillar [72]. Ergosterol peroxide is an ergostanoid derived from Ergosterol ($C_{28}H_{44}O_3$; MW: 428.6 g/mol) which has been isolated from fungi such as *Ganoderma carnosum* [73] and also *C. sinensis* [74]. Similarly, there are many other ergosterol type compounds found in *Cordyceps* spp. [75]. The pharmacological properties of the various *Cordyceps*-derived sterol compounds have been presented in Table 4.

Other sterols

Different sterol compounds, like: Fungisterol (Figure 3b – 08), β-sitosterol-3-O-acetate, Stigmasterol3-O-acetate, 4,4-dimethyl-5α-ergosta-8,24 (28)-dien-3β-ol,17(R)-17-methyllincisterol and β-sitosterol, were found in the ethanol extracts of *C. sinensis* [76]. In another study: hexadecanoic acid ergosterol-ester, docosanoic acid campesterol-ester, ergosterol and Ergosta-7,22-dien-3 were separated from ethylacetate and chloroform fractions of methanol extract of *C. jiangxiensis* mycelium [77]. Nine recognized sterols, such as: ergosterol peroxide, ergosterol, 3β,5α,9α-trihydroxy-(22E,24R)-ergosta-7,22-dien-6-one, 3β,5α,9α,14α-tetrahydroxy-(22E,24R)-ergosta-7,22-dien-6-one, 3β,5α,6β-(22E,24R)-ergosta-7,22-dien-3,5,6-triol, 3β,5α,6α-6- methoxyergosta-(22E,24R)-7,22-diene-3,5-diol, 4-hydroxy-17R-methylincisterol, 5α,6α-epoxy-(22E,24R)-ergosta-8(14),22-diene-3β,7α-diol and 9,11-dehydroergosterol peroxide, have been extracted from the spores and mycelia of cultivated *C. cicadae* [78].

Proteins

The total biomass has been reported to produce 29.1% to 33% of crude protein [11,79]. Proteins obtained from *Cordyceps* spp. are enzymes, including extracellular and intracellular proteases. CSDNase is an intracellular class II DNase (deoxyribonuclease) isolated from the *C. sinensis* cultured mycelia. It is a single chained 34 kDa protein and operates as a deoxyribonuclease on both ssDNA and dsDNA, but favorably on dsDNA. It exhibits the highest activity at pH 5.5 and a temperature of 55 °C [80]. Antimicrobial activity against: *Proteus vulgaris*, *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli,* and *Salmonella typhi,* has been exhibited by the *C. sinensis* Antibacterial Protein (CSAP) isolated from *C. sinensis*. However no effect was seen on fungal strains (*Mucor mucedo*, *Aspergillus niger* and *Penicillium citrirurn*) and yeast (*Candida* spp., *Saccharomyces cerevisiae* and *Hansenula anomala*) [80]. A 51 kDa fibrinolytic neutral protease obtained from *C. militaris* is most active at pH 7.4 and 37 °C. It has a high chymotrypsin substrate S-2586 specification that indicates that it is similar to a serine protease, such as chymotrypsin. It hydrolyzes the α-chain first, followed by the γ- and β-chains of fibrin [81]. Similarly, CSP, a31 kDa fibrinolytic serine protease has been reported from the culture supernatant of *C. sinensis*. It is an extracellular protease that has a free cysteine residue close to the active site that may hydrolyze bovine serum albumin (BSA) and, to a less significant extent, human serum albumin (HSA). It is a plasmin-link protease, and not a plasminogen activator, with a preference for cleaving the α-chains of fibrinogen and fibrin. It has been reported to exhibit its highest activity at pH 7 and a temperature of 40 °C. Hence, CSP can be used for cardiovascular illness, which will shed fresh light on the prospective novel remedial agent for the management of thrombosis [82]. Choi et al. [83] extracted a 34 kDa fibrinolytic protease from a Korean *C. militaris* that exhibited its highest activity at pH 7.0 and temperature 40 °C. It is more chymotrypsin-like serine metalloprotease, as it shows a preference for *N*-succinyl-Ala-Ala-Phe-p-nitroanelide, a synthetic substratum [83]. CML, a *C.militaris* lectin (31.0 kDa), demonstrated

Table 4. Pharmacological and therapeutic properties of sterols derived from *Cordyceps* spp.

Compound	Organism	Functions	References
Ergosterol	*C.militaris* (L) Link	*Anti-inflammatory effect* ↓ Nitric oxide production by LPS triggered inflammation in BV2 cells	[161]
Ergosterol peroxide	*C. cicadae*	*Anti-Fibrotic effect* - TGF-ß1-induced renal fibroblast multiplication and fibronectin synthesis were improved	[162]
5α,8α-epidioxy-24(R)-methylcholesta-6,22-dien-3β-D-glucopyranoside Ergosta-4,6,8(14),22-tetraen-3-one	*C. sinensis*	*Anti-tumor effect* - Inhibited tumor cell lines (HL-60, Jurkat, K562, RPMI-8226 and WM-1341) multiplication	[74]
5α,8α - Epidioxy-22E-ergosta-6,22-dien-3b-ol 5a,8a-epidioxy- 22E-ergosta-6,9(11),22-trien-3b-ol 5α,6α -epoxy- 5α -ergosta-7,22-dien-3b-ol	Cultured *C. sinensis* mycelium	Cytotoxic and apoptosis-inducing activities	[75]
Jiangxienone (5,6;9,10- disecoergosta-3,7,22-trien-5,9-dione-6,10-olide)	*C. jiangxiensis*	*Cytotoxicity* –Strong cytotoxic consequences on human gastric adenocarcinoma SGC-7901 cell and human lung carcinoma A549 cells.	[163]
H1-A	*C. sinensis*	*Apoptosis*-Curbs the increase of human mesangial cells by inhibiting the tyrosine phosphorylation of Bcl-2 and Bcl-XL	[164]

hemagglutination activity in mouse and rat erythrocytes, indicating that it has mitogenic activity toward mouse splenocytes [84]. A unique serine protease, Cordysobin, (31 kDa), was recently isolated from *C. sobolifera* dried fruiting bodies, which works at 10.0 pH and a temperature of 65 °C. Chymostatin and phenylmethylsulfonyl fluoride (PMSF) both suppressed this protease and this protease has shown considerable suppressive activity against HIV-1 reverse transcriptase (RT) [85].

Polypeptides

In addition to different proteases, *Cordyceps* produces polypeptides that play a vital part in clinical trials. Cordymin, an antifungal peptide of 10,906 Da molecular mass has been isolated from *C. militaris* [86]. Cordycedipeptide A (Figure 3b – 10) is another cyclopeptide obtained from *Cordyceps* whose composition was explained as 3-acetamino-6-isobutyl-2,5-dioxopiperazine [87]. The same group of researchers isolated other two potential peptides known as Cordyceamides A and B (Figure 3b – 11 and 12) from the liquid culture of *C. sinensis* [88]. The pharmacological effects of these compounds have been summarized in Table 5.

Amino acids

The major constituent amino acids that have been isolated from *Cordyceps* spp. Include: glutamate, arginine, and aspartate, while the amino acids with the best pharmacological importance were: argentine, glutamate, and tryptophan [89]. Tryptophan is a precursor of serotonin and acts as an effective hypnotic and sedative agent [90]. Glutamate has been reported to down-regulate and inhibits the immune system. Other amino acids reported from *Cordyceps* spp. includes: threonine, serine, proline, glycine, valine, methionine, leucine, isoleucine, histidine, and cysteine [90].

Fatty acids

Fatty acids do not constitute a major part of the bioactive component preset in *Cordyceps* spp. Docosanoic acid, lauric acid, linoleic acid, lignoceric acid, myristic acid, oleic acid, pentadecanoic acid, palmitoleic acid, palmitic acid, and stearic acid, and four free sterols, such as: campesterol, cholesterol, ergosterol and β-sitosterol have been found in various *Cordyceps* spp. Including: wild *C. gunnii, C. liangshanensis* and *C. sinensis*, as well as cultured *C. militaris* and *C. sinensis* [91]. Pressurized liquid extraction (PLE), trimethylsilyl (TMS) derivatization, and Gas chromatography-mass spectrometry (GC–MS) analysis were used to identify free fatty acids present in *Cordyceps* spp.

Other compounds

Cordycepic acid ($C_7H_{12}O_6$, 1,3,4,5-tetrahydroxycyclohexane-1-carboxylic acid) (Figure 3c – 16), a quinic acid isomer, was extracted from *C. sinensis* (Berkeley) Saccardo [92]. Sprecher and Sprinson later discovered the organization of the crystalline substance known as "cordycepic acid" [93] as D-mannitol. CA (Cordyceps acid) has the potential to suppress the growth of human lung cancer A549 cells implanted into nude mice, damage tumor cell structure, and increase tumor cell death. It is thought that the process is connected to Nrf2/HO1/NLRP3/NFB [94]. Ophiocordin, ($C_{21}H_{22}N_2O_8$, MW: 430) (Figure 3c – 14) is another molecule that was extracted from *C. ophioglossoides* submerged cultures and has been reported to exhibit antifungal properties against *Paecilomyces* TU 137 or *Mucor* TO 284 [95]. Another biomolecule, Bioxanthracenes ($C_{34}H_{36}O_{10}$) (Figure 3c – 15), from *C. pseudomilitaris* BCC1 620, has been reported to exhibit antimalarial property [96]. *C. militaris* fruiting bodies have a vivid yellow shade because of carotenoids. Dong et al. [97] extracted novel carotenoids from the fruit bodies of *C. militaris*, which were recognized as xanthophylls and called cordyxanthin-I,

Table 5. Pharmacological and therapeutic properties of different polypeptides derived from *Cordyceps* spp.

Compound	Property	Effect	References
Cordymin	Antifungal and Antiproliferative effect	Inhibited the fungi like *Bipolaris maydis*, *Mycosphaerella arachidicola*, *Rhizoctonia solani* and *Candida albicans*.	[86]
		Exhibited antiproliferative action toward MCF-7 breast cancer cells	
	Anti-inflammatory	↓TNF-α and IL-1β	[165]
		In a dose-dependent way, it hampered acetic acid-induced abdominal constrictions in mice	
		Hampers infiltration of polymorphonuclear cells and IR-induced up-regulation of brain assembly of C3 protein level, IL-1β and TNF-α	[166]
	Anti-diabetic activity	↓ALP and TRAP, Causes β cell recovery and decreases oxidative stress.	[167]
		Studies on diabetic osteopenic rats showed both anti-diabetic and anti-osteoporotic activity	
Cordycedipeptide A	Anti tumor	Cytotoxic activities - A375, HeLa and L-929 cell lines	[87]
Cordyceamides A and B			[88]

II, III and IV. The concentrations of 2 xanthophylls, β-carotene, and lycopene in *C. militaris* fruiting body extract were determined. The β-carotene and lycopene levels were 0.328 mg/g and 0.277 mg/g, respectively [98]. Similarly, two other peptides – Cicadapeptins I and II from *C. heteropoda* along with myriocin, have been reported to exhibit antibacterial activity along with limited antifungal activity [99]. Codypyridones A and B from *C. nipponica* have been stated to show *in vitro* antimalarial activity [100]. Three new unusual spirodecane sesquiterpenes - cordycepol A, cordycepol B, cordycepol C (Figure 3C – 17–19), and a new fumagillol analog, cordycol have been reported from *C. ophioglossoides* with an inhibitory effect on HeLa and HepG2 cell lines [101]. A cyclodepsipeptide cordycecin A (Figure 3b – 13) and four other compounds: beauvericin, beauvericin A, E and J have been reported from *C. cicada,* with considerable inhibitory activity on HepG2 and HepG2/ADM cells [102]. Three pigment compounds Cryptosporioptide A, Pinophilin C and Terreusinone A have been isolated from a solid culture of *C. gracilioides* and are reported to have inhibitory activity against the enzymes: PTP1B (Protein-Tyrosine Phosphatase 1B), SHP2 (Src homology region 2 domain-containing phosphatase-2), CDC25B (M-phase inducer phosphatase 2), LAR, and SHP1 that regulates cellular levels of protein tyrosine phosphorylation [103]. Three distinct cerebrosides - Cordycerebroside A, glucocerebroside, and soyacerebroside I, extracted from *C.militaris* have been found to prevent the buildup of pro-inflammatory iNOS protein and decrease the production of COX-2 protein in LPS-stimulated RAW264.7 macrophages [104]. Similarly, a compound called 4-Isopropyl-2,6-bis(1-phenylethyl)phenol (KTH-13) extracted from the butanol extracts of *C. bassiana* has shown antiproliferative activity against C6 glioma cells [105].

Various extracts

Apart from various pure compounds from *Cordyceps*, different pharmacological applications were checked for multiple extracts from *Cordyceps* biomass. According to Reis et al. [106], the methanolic extract of *C. militaris*: lowers lipid peroxidation, has reducing power and may scavenge free radicals, and has significant antibacterial and antifungal effects. Moreover, the extract inhibited the growth of human cancer cell lines: MCF-7 (breast), NCI-H460 (non-small lung), HCT-15 (colon), and HeLa (cervical) [106]. Antimicrobial properties of several ethanol extracts of *C. sinensis* were tested against *E. coli*, *P. aeruginosa*, and *B. subtilis*, and it was discovered that all of the extractions showed antimicrobial activity. However, the aqueous extract showed low inhibition [107]. Extruded products of cereal grains (EC) and EC combined with Cmilitaris (ECC) were gavaged to mice for 30 days to examine their anti-fatigue effects. The anti-fatigue activity was also assessed utilizing tests of fatigue-related markers and a weight-loaded swimming test. Researchers found that ECC improved glycogen depletion in mice by: increasing the availability of fatty acids and ATP levels, decreasing blood urea nitrogen (BUN) and malondialdehyde (MDA) levels, and increasing the levels of the anti-fatigue enzymes glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), and catalase (CAT) [108]. In mice, a water extract of *Cordyceps sinensis* (CS Extract) significantly increased blood testosterone and the weight index of reproductive organs. Furthermore, it promotes the proliferation of hormone-sensitive VCaP cells (rather than hormone-independent PC-3 cells) *in vitro* and *in vivo*, most likely through an increase in blood testosterone and the activation of AR [109]. Water extracts of *Cordyceps sinensis* inhibited T tumor formation in an orthotropic mouse tumor model in a dose-dependent fashion. *C. sinensis* may suppress tumor development by boosting macrophage polarization and increasing its activity by activating the NF-B signaling pathway [110]. The beneficial effect of *C. militaris* ethyl acetate extract on exercise performance was investigated in a study by conducting grip strength tests every week and biochemical analysis on blood samples after administration. CMEE showed an effect on biomarkers associated with the ATP production pathway but had no effect on muscular tiredness biomarkers. As a result, *C. militaris* may improve exercise performance, which may be due to an increase in ATP generation rather than a decrease in muscle exhaustion after exercise [111]. In mice that had been immunosuppressed by irradiation, *C. sine*sis aqueous extract (CSAE) was tested for its therapeutic properties. In the spleens of irradiated mice, CSAE increased Bcl-2 while decreasing Bax and cleaving caspase-3. CSAE was most likely linked to an antiapoptotic action as well as the modulation of adaptive immunity [112]. In A549 cells, *C. militaris* extract (CME), a hydrosoluble fraction, produced pyroptosis that caused cell bubbling and lysis, as well as inhibiting cell proliferation. P53 - downstream proliferative proteins, comprising: P53, P21, CyclinB1, CDC25B, Bcl-2, and BCL2 associated agonists of cell death, are suppressed by high concentrations of CME (200 g/ml), which arrests G2/M and G0 cell cycles. CME promoted caspase-3-dependent apoptosis and pyroptosis in A549 cells *via* the caspase-3/PARP and caspase-3/GSDME pathways [113]. Eiamthaworn et al. [114] used aqueous and ethanolic extracts of *C. militaris* against pathogenic bacteria that cause human skin illnesses, such as: *Cutibacterium acnes*, *Staphylococcus*

aureus, *Pseudomonas aeruginosa*, and methicillin-resistant *S. aureus* (MRSA). They even noted the anti-oxidant qualities of these extracts [114]. *In vivo* studies of the effects of water-soluble, carotenoid-rich *C. militaris* extracts on the function of light-damaged mice retinas were conducted by Chen et al. (2022). Administering this *C. militaris* extract orally (10 mg/kg, twice daily): decreased Müller cell hypertrophic gliosis, increased GSH levels, and encouraged the recovery of symptoms of retinal degenerative diseases - loss of visual acuity (VA) and visual contrast sensitivity function (VCSF) thresholds, notably for high spatial frequency-characterized vision, to protect neural retina tissue from light-evoked photoreceptor cell death [115]. The solid-based residues (SBRs) left over after harvesting the fruiting bodies of grown *C. militaris* P-1-012 were examined for potential application in cosmetics. According to LC-QTOF- MS/MS analysis, the crude SBR extracts (ethyl acetate, acetone, ethanol, hot water) included: nucleosides, nucleobases, amino acids, peptides, sugars, phospholipids, alkaloids, organic acids, and vitamins. As a result, SBRs are appealing materials for the future development of new active compounds in cosmetics and associated sectors. Furthermore, antioxidant and tyrosinase inhibitory activities, photoprotection, and cytotoxicity were assessed [116].

Efficacy and safety of *Cordyceps*

As stated in the preceding sections, many bioactive metabolites derived from these fungi have shown various beneficial or medicinal actions. *Cordyceps*' tremendous worldwide interest and value has resulted in a wide range of commercial items developed from these fungi all over the world. Table 6 will provide an overview of numerous enterprises producing *Cordyceps*-related items, such as: capsules, fruiting bodies, tea bags, gummies, and so on in countries, such as: India, China, the United Kingdom, and the United States of America. To address concerns about using these fungi as food supplements or health additions, safety studies are necessary.

Animal model studies

In animal models few studies were reported for the safety of *Cordyceps* spp. Oral administration of grown fruiting body of *O sinensis* (FBOS) was administered for 28 days and tested for sub-acute toxicity in Sprague Dawley rats at doses up to 1000 mg/kg by The results of hematology and serum biochemistry showed that grown FBOS therapy had no harmful impact [117]. Similarily, the chromosomal aberration test of: Chinese hamster lung (CHL) cells, Ames test, acute toxicity test, and micronucleus (MN) test of bone marrow cells in ICR mice were used to assess the toxicological safety of the grown Chinese *Cordyceps*. Within 14 days, no animal mortality or aberrant changes in general dissection of numerous tissues and organs of the animals were discovered. Based on the findings of four toxicological studies, it was shown that farmed Chinese *Cordyceps* was non-toxic in a single intragastric injection at large dosages in mice [118].

Table 6. Different products produced from *Cordyceps* spp. in different countries.

Country	Company	Website (Access date : 23 April. 2023)	Products	Function
India	Mycoforest	www.mycoforest.com	Biomass powder, Tincture, Tea bags	Immune Enhancer
	Real Mushrooms	www.realmushrooms.com	Capsules	Peak performance
	Biotrex Nutraceuticals	http://bio-trex.com	Capsules	Energy Booster Strengthens Immune System Supports Heart Health
United Kingdom	Shroomex	www.shroomex.com	Capsules	Energy and Endurance
	Hybrid Herbs	www.hybridherbs.co.uk	Biomass powder	Promote vitality and improve athletic performance
United States of America	Cure mushrooms	www.curemushrooms.com	Tinctures, Gummies	Energy and Performance
	Double wood supplements	doublewoodsupplements.com	Capsules	Healthy Aging Athletic Performance Cardiovascular Health
	Noomadic	www.noomadics.com	Capsules	Energy and Endurance, Immune support
	Oregons wild harvest	www.oregonswildharvest.com	Capsules	Endurance and stamina support
China	Hunan MT health Inc.	www.instant-tea-powder.com	Powder	Improve immunity
	Tiens	www.tiens.com	Capsules	Food supplement
	Ganoherb technology(Fujian) corporation	www.organicreishi.gongwong.com	Capsules	Supports respiratory cardiovascular and immune health
	Shenzhen Evergreen Bio-Health Technology Co., Ltd.	www.egbioh.en.china.cn	Capsules	Immune system, Anti-fatigue; Kidney tonic, Improve men health

Human trials

Some Human trails were also conducted to assess the safety of *Cordyceps*. The effectiveness and safety of *C. militaris* for increasing cell-mediated immunity were investigated in healthy male adults by administering 1.5 g/day of ethanol-treated *C. militaris* in capsules for four weeks. The natural killer (NK) cell activity, lymphocyte proliferation index (PI), and T-helper cell 1 (Th1) cytokine cluster (interferon [IFN]-c, IL-12, IL-2, and TNF-a were measured after 4 weeks and found that *C. militaris* increased NK cell activity and lymphocyte proliferation while decreasing Th1 cytokine secretion. It was concluded that *C. militaris* is both safe and effective for boosting cell-mediated immunity in healthy male adults [119]. Jin Young Heo et al. [120] investigated the effectiveness and safety of *C. militaris* in Korean people with moderate liver dysfunction by giving 1.5 g of *C. militaris* per day (2 capsules per dose, twice per day). The mean ratio of change of Hounsfield unit of 8 segments of liver rose by an average of 21.43–45.11% in the *C. militaris* group and 9.64–11.41% in the placebo group in an examination of the liver CT scan at 8 weeks after administration compared to baseline. Others revealed no statistically significant difference between groups. This suggests that *C. militaris* extract may be used safely as a functional food in individuals with moderate liver disease, and that it may protect against the advancement of fatty liver or cirrhosis by suppressing lipid buildup in hepatocytes [120]. Wesley David Dudgeon et al. [121] investigated the *C. Militaris* containing mushroom mixture supplementation (PeakO2) in a randomized, placebo-controlled, single-blind research including 43 young adult volunteers. The findings imply that longer-term, lower-dose PeakO2 supplementation appears to increase endurance performance in otherwise healthy young people. Also, short-term supplementation with larger doses of PeakO2 may boost performance, although the results may vary depending on fitness level [121]. You-Shan Tsai [122] conducted a Randomized Clinical Trial with 49 volunteers to assess the safety of HEA-enriched *C. cicadae* mycelium. During three months, the participants were given 1.05 g of freeze-dried *C. cicadae* mycelium granules once a day. Their blood samples were obtained for examination at the start and end of the trial. There were no significant variations in renal and hepatic function between the baseline and final assessments. There was also no effect on blood electrolytes or blood lipid levels. There were no side effects or negative sensations stated by participants during clinical observation, indicating that *C. cicadae* mycelium generated *via* liquid fermentation is safe and may be developed as a functional health food [122]. Further elucidation of the compounds, as well as detailed analysis of metabolite bioactivity and chemical safety, will make it possible to utilize *Cordyceps* fungus as human food or alternative medicine safely.

Conclusion

The species of *Cordyceps* are currently understudied, the evidence indicates that they are gold mines for unparalleled new drug research. Due to people's preference for natural herbal treatments, making use of *Cordyceps* as a natural therapeutic mushroom is inescapable. Despite the enormous possibilities of novel medicines, there are still significant gaps in this genus. First, most investigations carried out to date focus only on *C. sinensis* and *C .militaris*. No extensive analyses of the phytochemical and biological activity of the other species have been studied in detail. It is very important to identify and explore alternatives that are equally effective as *C. sinensis*, such as *C. militaris* and its associated species, because of the high research expense and the rarity of *C. sinensis*. This might result in the discovery of additional bioactive components with various other therapeutic applications. Furthermore, new techniques and technology for extraction and evaluation of the components, including: biological screening, phytochemical specific analysis, and clinical studies, have to be evaluated along current scientific lines. Modern biotechnological methods would be considered necessary to further boost the bioactive potential of metabolites. Instead of extrapolating *in vitro* results to show the therapeutic efficacy of this species, the molecular mechanisms of action of bioactive components and crude extracts must be thoroughly characterized. Further research is needed to get a mechanistic understanding of the mysterious potential of this therapeutic fungus on human health, as well as to promote cultivation tactics for commercialization and ethno-pharmacological usage of this remarkable fungus.

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